A Computational Library of the Biomolecular Targets for Toxicity: Receptors in the Endocrine System

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Many program offices face the problem of assessing the potential health effects of large numbers of chemicals. In some cases, there is little data relative to the biological effects of the specific chemical of interest. One approach to problems of this type is to extrapolate from the extant data to the information required using structure activity models. These models are usually developed from bioassay data for a series of (similar) chemicals. Often, they are based on the structure, properties, and reactivities of the chemicals that have been tested, and untested chemicals are evaluated based on these properties. Information about the biological system that is being assayed or the putative mechanism for toxicity may influence the selection of the parameters in the model, but is not specifically included in the model. Advances in a number of different fields have made it possible to include the biological system being assayed directly in the model. First, there has been an increase in the molecular level data about the mechanisms of toxicity; in many cases, the biomolecular targets for toxicity and the molecules responsible for key transformation steps have been identified. Second, the methods for determining the three-dimensional structure of macromolecules have been improved and, to some extent, become routine. As a result, the structures of many biomolecular targets of toxicity have been determined. Third, a great deal of molecular modeling software has become available for characterizing the interaction between biopolymers and small molecules. Much of this software was developed for the design of new pharmaceuticals. Fourth, highly parallel computers have become available; in many ways, these problems are naturally parallel. In order to apply these advances to an Agency problem, the capacity of molecules to bind to the estrogen and androgen receptor is being modeled. Crystal structures for these receptors with ligand bonds are in the literature. The ligand is removed by computational means to create a target for potential environmental ligands. The capacity of an untested chemical to bind to the receptor may be estimated from its best fit to the target. A number of crystal structures of the estrogen receptor with different ligands and cofactors bound are available in the literature. Studies comparing the results for different estrogen receptor targets created from these crystal structures show the importance of including receptor flexibility in the model. There are only a few structures available of the androgen receptor. In this case, flexibility must be included directly, which is a much more computer-intensive modeling effort. All of these results will be shown. Ultimately, a library of biomolecular targets for toxicity will be developed.